Anja Reichenbach

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

	Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2005/050708	17.02.2005	18.02.2004

International Patent Classification (IPC) or both national classification and IPC
C07D221/12, A61K31/473, A61P11/00, A61P29/00, A61P37/02

Applicant
ALTANA PHARMA AG

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2005/050708

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 13,14

because:

☒ the said international application, or the said claims Nos. 13, 14 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-14
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	1-14
Industrial applicability (IA)	Yes: Claims	1-12
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

re item III:

Claims 13 and 14 have to be considered as being directed to the treatment of the human and/or animal body. Under the terms of Rule 67.1 and Art. 34 (4)a)i) PCT the International Preliminary Examination Authority is not required to carry out an examination on such claims.

re item V:

1. Prior art

The examining procedure is based on the documents cited in the International Search Report:

D1: WO 2004/018431 A (WEINBRENNER STEFFEN ; SCHMIDT BEATE (DE); ALTANA PHARMA AG (DE); FLOCK) 4 March 2004 (2004-03-04)
D2: WO 02/066476 A (BYK GULDEN LOMBERG CHEM FAB ; FLOCKERZI DIETER (DE)) 29 August 2002 (2002-08-29)
D3: US-B-6 306 869 B1 (FLOCKERZI DIETER) 23 October 2001 (2001-10-23)
D4: US-B-6 476 025 B1 (GUTTERER BEATE) 5 November 2002 (2002-11-05)

2. Novelty

The present 6-(urea substituted)phenylphenanthridine derivatives differ from the 6-(urea substituted)phenylnaphthyridine derivatives according to D2 and D3 by the replacement of a nitrogen by a carbon atom in the tricyclic moiety and from the 6-(substituted)phenylnaphthyridine derivatives according to D3 additionally by the urea group instead of an amide group as substituent of the phenyl residue in position 6. The present compounds differ structurally from the 6-(substituted)phenylphenanthridine derivatives according to D4 only by the urea group instead of an amide group as substituent of the phenyl residue in position 6. Thus the subject matter of claims 1 to 14 is considered to fulfil the requirements of Art. 33 (2) PCT with respect to documents D2 to D4.

3. Inventive step

Documents D2 and D3 are concerned with 6-(substituted)phenylnaphthyridine derivatives and D4 is concerned with 6-(substituted)phenylphenanthridine derivatives which all are potent inhibitors of phosphodiesterase (PDE) IV as are the 6-(substituted)phenylphenanthridine derivatives of the present application. The naphthyridines of D3 and the phenanthridines of D4 have the same substituents in the phenyl residue in position 6, inter alia amides. The structural closest prior art showing the at least qualitatively the same pharmacological activity is to be seen in document D2, since these compounds, bearing also the essential urea substituent in the phenyl group in position 6 differ merely by the naphthyridine instead of the phenanthridine residue, i.e. a nitrogen has been replaced by a carbon in the present compounds.

If the problem underlying the present application were to be seen in provision of further PDE IV inhibitors, the solution of the problem must be considered as being obvious for the following reason:

From the relevant prior art documents D3 and D4 it was known that the replacement of the tricyclic naphthyridine moiety (D3) by the tricyclic phenanthridine moiety (D4) both substituted in the phenyl residue in position 6 by an amide does not change the PDE IV inhibitory activity, since both types of compounds are potent inhibitors of PDE IV. Thus it was completely obvious for the skilled person to try this exchange with 6-(urea substituted)phenylnaphthyridines as known from D2 as well to result with the claimed 6-(urea substituted)phenyl phenanthridine derivatives.

Therefore, re that very close prior art (structurally and concerning activity), the problem underlying the present application, the solution of which could involve an inventive step, is therefore to be seen in the provision of compounds that exhibit an unexpected or surprising effect as compared to the structural closest prior art compounds according D2. The Applicant's attention is drawn to the fact, that any comparative tests should be made with compounds of the closest prior art, showing the closest possible structural similarity, differing structurally only in the essential feature, i.e. only in the feature which renders the subject matter novel and which an inventive step may be based on. If such an effect could be demonstrated (preferably by concrete experimental data) an inventive step might be

acknowledged at least for the specified or exemplified compounds of the present application. And, in this case the breadth of the claims appears to be acceptable since in principle known from the closest prior art D2.
As yet, the subject matter of claim 1 and the dependent ones does not fulfil the requirements of Art. 33 (3) PCT.

4. Industrial applicability

No objection arises with respect to claims 1-12, since the claimed compounds may be used for the production of pharmaceutical compositions.

re item VI:

It is brought to the Applicant's attention, that the part of document D1 as cited above and entitled to its EP priority if entering the European phase, were relevant for the consideration of novelty and inventive step. This document were novelty destroying with the disclosure of claims 1 to 13 and explicitly novelty destroying for present claims 1 to 14 with the disclosure of its 13 examples.